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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
1 September 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MIXTURES OF CALCITONIN DRUG-OLIGOMER CONJUGATES AND METHODS OF USE IN PAIN TREATMENT

(57) Abstract: A mixture of conjugates in which each conjugate in the mixture comprises a calcitonin drug coupled to an oligomer that includes a polyalkylene glycol moiety is disclosed. The mixture may lower serum calcium levels in a subject by 10, 15 or even 20 percent or more. Moreover, the mixture may be more effective at surviving an *in vitro* model of intestinal digestion than non-conjugated calcitonin. Furthermore, the mixture may exhibit a higher bioavailability than non-conjugated calcitonin. The compositions of this invention are useful in the treatment of various bone disorders and pain.

WO 2005/004792 A3

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
MARY L. MILLER
MYERS BIGEL SIBLEY & SAJOVEC, P.A.
P.O. BOX 37428
RALEIGH, NC 27627

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	25 JUL 2005
Applicant's or agent's file reference 9233.114.WO	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/16784	27 May 2004 (27.05.2004)	24 June 2003 (24.06.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07K 1/113, 14/535, 7/00: A61K 38/00 and US Cl.: 530/, 307, 351, 313, 345; 514/2, 3, 8, 12, 13

Applicant

NOBEX CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Samuel W Liu Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/16784

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/16784

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-13	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-13	NO
Industrial applicability (IA)	Claims 1-13	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/16784

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-13 lack inventive step under PCT Article 33(3) as being obvious over Ekwuribe et al. (US 2003/0060606), Camble et al. (US Pat. No. 5773581), Lee et al. (Pharm. Res, (1999) 16, 813-818) (A), Lee et al. (Pharm. Res. (2002) 19, 845-851) (B), and Lucke et al. (Biomaterials (2000) 21, 2361-2370).

In the patent claims 33-72, Ekwuribe et al. teach a method of treating a disease state, e.g., osteoporosis Paget's disease comprising administering to a subject a calcitonin conjugated with polyethylene glycol (PEG), wherein the PED moieties are linked to lysine residues 11 and 18 (see the patent claims 44). Since it is well-known fact that Paget's disease is a chronic bone disorder that typically results in enlarged, deformed bones and may result in bone pain (a peripheral pain), arthritis, the Ekwuribe's teaching is applied to claims 1-2. Also, Camble et al., Lee et al.(A), Lee et al. (B), and Lucke et al. teach the subject matter of the instant claims 1-2.

In the patent claims 45 and 50, Ekwuribe et al. teach that the PEG moiety consists of 7 PEG subunits (i.e., -$[CH_2CH_2O]_7$-), which is covalently linked to a carboxylic acid moiety, as applied to claims 3-4.

In the patent claim 51, Ekwuribe et al. teach the same structure of claim 5, as applied to the instant claim 5.

In the patent claim 49, Ekwuribe et al. teach the same structure of claim 6, as applied to the instant claim 6.

In the patent claims 46 and 51, Ekwuribe et al. teach the same structures of claims 7 and 8, respectively, as applied to the instant claims 7-8.

In the patent claims 52, 54, 55 and 56, Ekwuribe et al. teach the same structures of claims 9, 10. 11 and 12, as applied to the instant claims, 9, 10, 11 and 12.

In the patent claim 57, Ekwuribe et al. teach the same structure limitations as the formula A of the instant claim 13, which is applied to claim 13.

Ekwuribe et al. do not expressly teach the said method is applied to treating peripheral pain in said subject.

May et al. teach use of calcitonin or calcitonin gene related peptide for treating peripheral pain (see [0054]) and indicate that this has been known in the art, which is applied to the instant claims 1-13.

It would have been obvious to one skilled in the art at the time the invention was made to develop the method of treating peripheral pain comprising administering to said subject the PEG polymer or polyalklene glycol conjugated calcitonin peptide. The one skilled in the art would have been motivated to do this because (i) calcitonin has been suggested for use in treating peripheral pain condition. and (ii) as stated above, the osteoporosis Paget's disease typically results in enlarged, deformed bones, i.e., arthritis pain - a peripheral pain condition; hence, treatment of osteoporosis Paget's disease by the Ekwuribe's PDE-conjugated calcitonin would have

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

unavoidably led to treatment of the peripheral pain because the said pain is caused by the mentioned Paget's disease state. Thus, one skilled in the art would have readily and successfully arrived at the claimed process of the current application.

Claims 1-13 meet the requirement of PTC article 33(4), because the claimed process is useful for treating peripheral pain condition thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/16784

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07K 1/113, 14/535, 7/00: A61K 38/00
US CL : 530/, 307, 351, 313, 345; 514/2, 3, 8, 12, 13
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/, 307, 351, 313, 345; 514/2, 3, 8, 12, 13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/0060606 A1 (EKWURIBE et al.) 27 March 2003 (27.03.2003), abstract, claims 1-172 and [0011]-[0052].	1-13
Y	US 6,506,730 B1 (LEE et al.) 14 January 2003 (14.01.2003), abstract, columns 5-11 and claims 1-18.	1-2
Y	US 5,773,581 A (CAMBLE et al.) 30 June 1998 (30.06.1998), columns 3-5 and 11-14, Examples 27-28.	1-2
Y	LEE et al. Isolation, Characterization, and Stability of Positional Isomers of Mono-PEGylated Salmon Calcitonins. Pharmaceutical Research, 1999, Vol. 15, No. 6, pages 813-818. Entire document.	1-2
Y	LEE et al. Preparation and Characterization of Mono-PEGylated Epidermal Growth Factor: Evaulation of in Vitro Biologic Activity. Pharmaceutical Research. June 2002, Vol. 19, No. 6, pages 845-851. Entire document.	1-2
Y	LUCKE et al. Biodegradable poly(D,L-lactic acid)-poly(ethylene glycol)-monomethyl ether diblock copolymers: structures and surface properties relevant to their use as biomaterials. Biomaterials. December 200, Vol. 21, pages 2361-2370. Entire document.	1-2 and 13

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
17 July 2005 (17.07.2005)

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25 JUL 2005

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/16784

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LEE et al. Polymeric nanoparticle composed of fatty acids and poly(ethylene glycol) as a drug carrier. International Journal of Pharmaceutics. January 2003, Vol. 251, pages 23-32. Entire document.	4-12
Y,P	US 2003/0153488 A1 (MAY et al.) 14 August 2003 (14.08.2003), paragraph [0054].	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/16784

Continuation of B. FIELDS SEARCHED Item 3:
Databases: Medline, US Pre-Grant publication Full-Text database, US Patent Full-Text database, EPO Abstracts database, JPO Abstracts database, Derwent World Patent Index, and, issued patents AA, pending patents AA and Genebank (for sequence search).
Search terms: calcithonin, conjugate, polyethylene glycol (PEG), polymer, lysine and polyalkylen glycol.